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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

Influence of age at seizure onset on the acquisition of neurodevelopmental skills in an SCN8A cohort

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Abstract

Objective: To characterize a cohort of patients with SCN8A-related epilepsy and to perform analyses to identify correlations involving the acquisition of neurodevelopmental skills.

Methods: We analyzed patient data (n = 91) submitted to an online registry tailored to characteristics of children with *SCN8A* variants. Participants provided information on the history of their child's seizures, medications, comorbidities, and developmental skills based on the Denver II items. Spearman rank tests were utilized to test for correlations among a variety of aspects of seizures, medications, and neurodevelopmental progression.

Results: The 91 participants carried 71 missense variants (41 newly reported) and three truncating variants. Ages at seizure onset ranged from birth to >12 months of age (mean ± SD = 5 months 21 days ± 7 months 14 days). Multiple seizure types with multimodal onset times and developmental delay were observed as general features of this cohort. We found a positive correlation between a developmental score based upon percentage of acquired skills and the age at seizure onset, current seizure freedom, and initial febrile seizures. Analyses of cohort subgroups revealed clear distinctions between patients who had a single reported variant in *SCN8A* and those with an additional variant reported in a gene other than *SCN8A*, as well as between patients with different patterns of regression before and at seizure onset.

Significance: This is the first study of an SCN8A patient cohort of this size and for which correlations between age at seizure onset and neurodevelopment were investigated. Our correlation studies suggest that variants of uncertain significance should be considered in assessing children with SCN8A-related disorders. This study substantially improves the characterization of this patient population and our understanding of the neurodevelopmental effects associated with seizures for SCN8A patients, and provides a clinical context at initial presentation that may be prognostic for developmental outcome.

KEYWORDS
age at seizure onset, childhood epilepsy, developmental delay, neurocognitive skills

1 | INTRODUCTION

Mutations in a large set of genes have been implicated in early infantile epileptic encephalopathy, several of which are within voltage-gated ion channels. The first epilepsy case involving *SCN8A*, one of nine genes that encode voltage-gated sodium channels, was published in 2012.[1] Since the publication of this index case, the number of known cases of SCN8A-related epilepsy has grown, with >80 published reports and many more unpublished cases.[2] Initially, *SCN8A* variants were found to be associated with intractable epilepsy and with seizure onset occurring within the first 18 months of life.[3] When seizures begin in infancy, the severity of outcome can range from "benign" cases, in which children outgrow their seizures and continue with a normal developmental profile, to "severe" cases of epileptic encephalopathy.[4] With the reporting of an increasing number of cases, it has become clear that the phenotypic spectrum of SCN8A-related disorders is much broader than initially perceived.[5] Not all variants are associated with intractable seizures, and for those that are associated with seizures there is a range of developmental features and comorbidities.[3] It is also becoming evident that certain amino acid positions are susceptible to more severe forms of encephalopathy.[3,5] At the same time, phenotypic manifestations, including neurocognitive development, can vary even when patients share the same causative amino acid variant.

Many factors (eg, age of seizure onset, pharmacoresistance) have been shown to influence the extent to which seizures impact neurocognitive development of children. For example, in the SCN8A population, age at seizure onset ranges from birth to >10 months of age, with an average onset time of 4.5 months.[3] Notably, the age of seizure onset has been reported to correlate with cognitive development.[6–10] Given the scope of critical developmental processes that occur between birth and 2 years of age,[9,11,12] seizures typically begin when the brain is particularly vulnerable. Given the variability in seizure characteristics among children, clinicians and parents are often at a loss to determine which factors are most influential in the overall growth and development of the child. This study is one of the first of its kind to examine associations between seizure characteristics and neurodevelopment in children with SCN8A-related epilepsy.

Here, we characterize a cohort of 91 patients whose caregivers participated in an online SCN8A registry. The registry contains data collection tools tailored to the features of SCN8A patients and includes Denver II items to more precisely capture variables that influence developmental outcome.[13] Our registry data include previously unreported *SCN8A* variants and phenotypes that expand our understanding of the neurodevelopmental spectrum of this population.

Key Points

- The percentage of SCN8A children acquiring late-learning skills (after 12 months of age) decreases
- Positive correlation of skill acquisition with seizure onset, seizure freedom, and initial febrile seizures is seen in this cohort
- There is a clear distinction for children with a single reported variant in *SCN8A* versus those with an additional variant reported in a gene other than *SCN8A*
- Development delays or regression prior to and/or at seizure onset affects skill acquisition patterns

We present analyses aimed at assessing the strength of associations involving the acquisition of developmental skills.

2 | MATERIALS AND METHODS

2.1 | Participant recruitment

An online SCN8A community registry was established at the University of Arizona (https://www.SCN8A.net). This registry is a secure database for parent/guardian-reported genotypic and phenotypic data for individuals with SCN8A epilepsy or SCN8A-related disorders. Responses from all participants who consented and enrolled in the registry and who completed questionnaires during the time period January 2016 to February 2018 were analyzed and compared for this study. The registry was approved by the University of Arizona Institutional Review Board, and informed consent was obtained from all participants.

2.2 | Data collection

All data were reported by parents or guardians of a child with an *SCN8A* variant through a questionnaire made available to members of the SCN8A community website. The entire questionnaire was designed to take 2-3 hours to complete and allowed the participants to submit copies of their child's medical records and genetic reports. Statistical analyses were based on seven questions that required yes/no responses, as well as multiple choice answers concerning initial seizure characteristics, and medication history.

2.3 | Development score

Using the Denver II test as a guide, 25 skills were chosen, six to seven from each category (fine motor, gross motor, social motor, and language), and participants were asked whether

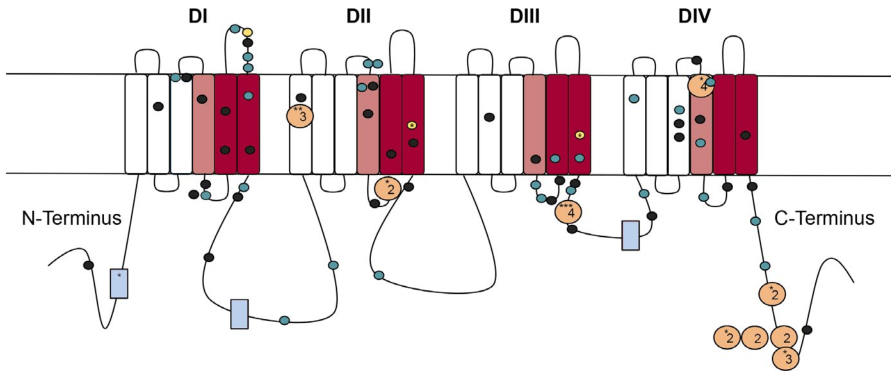

FIGURE 1 Schematic representation of SCN8A channel and variants present in cohort. The approximate positions of missense (circles) and truncating (rectangles) variants are shown. Missense variants present in the 8A group are shown in black circles, whereas those in the 8A+ group are shown in teal. Known loss-of-function variants are shown in yellow. Recurrent missense variants and the number of recurrence events are shown in light orange. The number of asterisks indicates the number of 8A+ recurrent, truncating, and loss-of-function variants

their child had acquired the skill. The percentage of skills acquired was calculated for each skill type and then averaged across all the four skill sets to create a developmental percentage. The assessment of each child was based solely on those skills generally achieved by 90% of the general population by the time of the age of the child. From the total averaged percentage, a development score (DS) from 1 to 5 was constructed (Table S1).

2.4 | Data analysis

A retrospective analysis of the registry data was performed. All genetic variants that were collected were mapped based on the canonical transcript (NM_001184880.0; Table S2). Data were analyzed using R statistical software.[14] Spearman rank correlation coefficient was used to assess pairwise relationships between particular seizure characteristic variables and DS. For the correlations, an absolute value of 0-0.1 was considered a very weak relationship, >0.1-0.3 was a weak relationship, >0.3-0.5 was a moderate relationship, and >0.5-1.0 constituted a strong relationship. Ordinal logistic regression was conducted to investigate additional factors beyond age at onset that had a significant impact on overall neurodevelopment and to confirm significant variables that were used in correlation analyses (Appendix S1).

3 | RESULTS

3.1 | Cohort characteristics

In our cohort of 91, there were a total of 71 missense variants, 41 of which have not been previously published (Figure 1). Of the missense variants, nine are recurrent with one variant present in four cases. The cohort also included three truncating variants (<4%), consisting of one frameshift, one nonsense, and one splice site variant. There also was a single in-frame deletion variant that resulted in a substituted amino acid at position 360. One participant did not know the exact position of the *SCN8A* variant; however, data from this case was included in the phenotypic analyses described below.

3.2 | Phenotypic manifestations

Less than 5% of participants (4/91) never presented with a seizure. The remaining 87 participants reported onset times ranging from birth to 50 months (mean $\pm$ SD = 5 months 21 days $\pm$ 7 months 14 days). Nearly a quarter of patients (21/91) reported a first seizure in the neonatal period, whereas 15% (14/91) reported an onset time > 10 months. Participants were currently taking an average of 2.5 $\pm$ 1.1 antiepileptic drugs (AEDs; not including rescue medications), with only nine children on a single AED.

Five families reported that their child had passed away (Table S4). Two apparently had died as a result of respiratory or other organ failure, whereas three met the criteria for sudden unexplained death in epilepsy (SUDEP). These children had seizure onset times ranging from 2 to 10 months of age and lived until the ages of 6 years 11 months, 7 years 8 months, and 15 years 1 month (Table S4). The two children who died as a result of organ failure had seizure onset times that were earlier than the three candidates for SUDEP and were younger at the time of death (Table S4). The neurodevelopmental skills of the SUDEP candidates varied, with DS ranging from 4.5 to 1.

3.3 | Developmental skills

All children in this cohort were delayed in some manner and did not achieve all skills by the median age as defined by the Denver II Screening Test. In the cohort of 91 children, 71 parents (78%) reported that their child did not experience age-appropriate neurodevelopment. Figure 2A

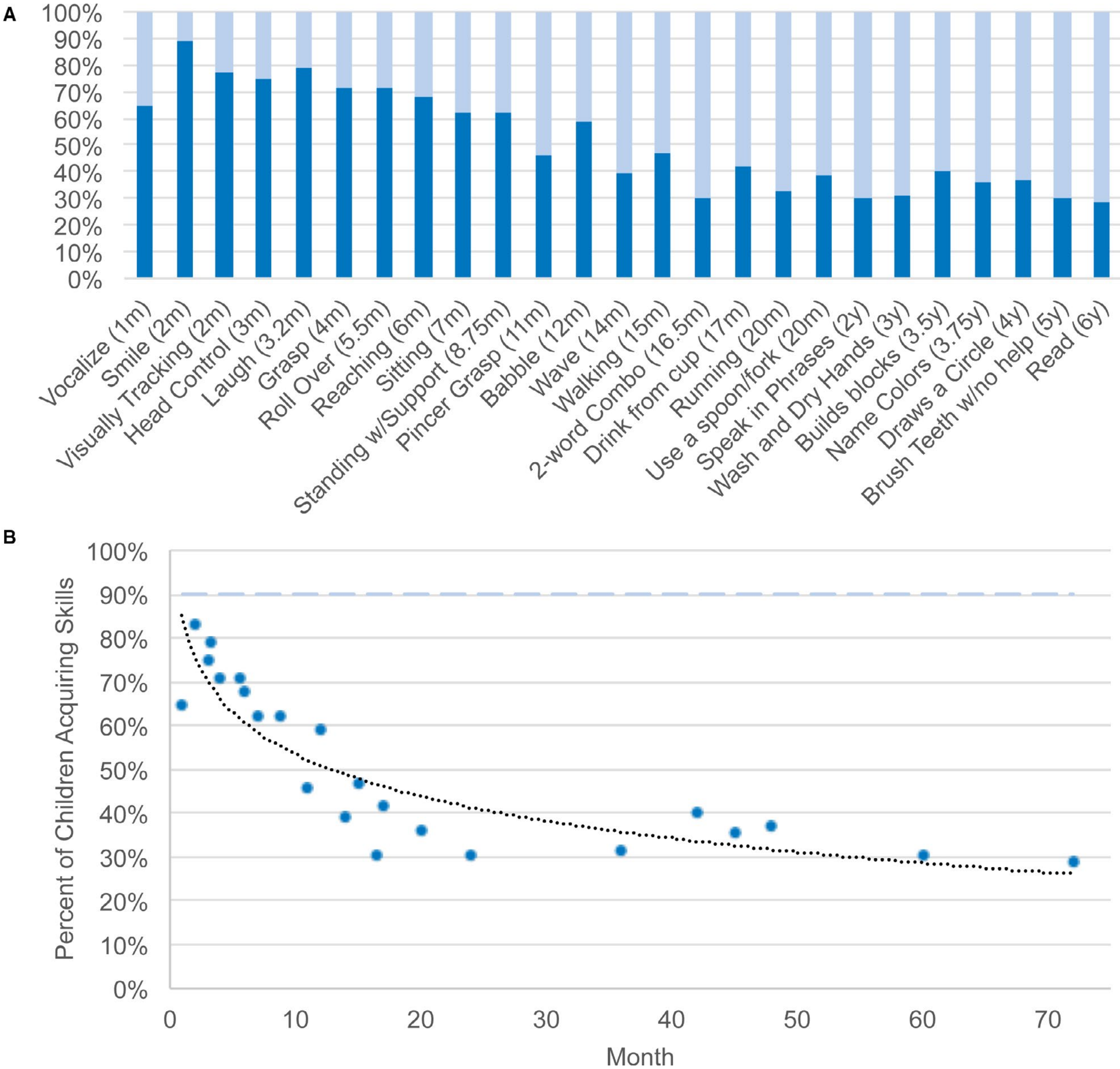

FIGURE 2 Development history. A, The percentage of children from the cohort who had acquired a particular skill (navy blue bars) versus those who had not acquired the skill (light blue bars). Skills are listed in chronological order of acquisition based on the Denver II. B, Percentage of children acquiring the Denver II skills from A were graphed along a continuous timescale (in months) from birth until 6 years of age. The horizontal dashed blue line reflects the 90th percentile of children who have acquired the skill by the appropriate time. A logarithmic trend (black dotted line; % skill gained = â + ĉ ln [age]) line is included to show the trend of lowered skill acquisition as developmental time increases

displays each of the Denver II milestones included in the questionnaire. Figure 2B shows that as age increases, the percentage of SCN8A children acquiring these later-learned milestones decreases.

3.4 | Ordinal logistic regression analyses

We used ordinal logistic regression to address two basic questions associated with overall neurodevelopment. First, what additional information beyond age at onset (ie, having an additional genetic variant, delay before or after seizure onset, seizure freedom of a minimum of 6 months, and febrile seizures as the initial seizure type) has a significant impact on development? Ordinal response variables were obtained by categorizing children into three development levels based on their overall DS, with 1 assigned to children with 0%-50% overall skill gain, 2 assigned to children with >50%-75% skill gain, and 3 to children with >75% skill gain. Notably, each month's delay in seizure onset leads to an improved predicted neurodevelopmental outcome, with a log odds of 0.195. For those children having a delay before seizure onset, their predicted development is reduced, with a log odds of 1.390. On

TABLE 1 Correlations shown for development score

	n	Seizure onset	Seizure freedom	Febrile seizures	AEDs, n
All patients	86	0.342*	0.302*	0.255**	−0.228**
8A	49	0.452*	0.326**	0.401*	−0.294**
8A+	37	0.067	0.266	0.087	−0.088

Note: Correlations were analyzed with Spearman rank tests and are displayed above.
Abbreviation: AED, antiepileptic drug.
***P* = <.01-.001, **P* = .05-.01.

the other hand, for those children who were seizure-free for 6 months at the time of the survey, their predicted development is improved, with a log odds of 1.044. Interestingly, the presence or absence of febrile seizures had the largest predicted impact (log odds = −1.510) and was marginally statistically significant ($P = 4.76 \times 10^{-2}$), likely as a result of a small number of patients experiencing febrile seizures (n = 11).

3.5 | Statistical correlations and acquisition of neurodevelopmental skills

We used Spearman rank tests to assess the correlation of four variables (Table 1) with DS. These analyses included 86 children from the cohort. We excluded five individuals, one due to internal inconsistency in their answers, and four because the child never had a seizure. We first examined the association between age at seizure onset and DS and found there to be a significantly positive correlation (Spearman correlation [SC], ρ = 0.342, $P = 1.34 \times 10^{-3}$; Table 1). We found a statistically significant positive correlation between DS and whether a child was seizure-free for a minimum of 6 months at the time of filling out the questionnaire (SC, ρ = 0.302, $P = 4.76 \times 10^{-3}$), and a weak positive correlation between DS and whether a child had a febrile seizure (ie, as opposed to generalized, partial, epileptic spasms) as the first seizure type at onset (SC, ρ = 0.255, $P = 1.75 \times 10^{-2}$). We found a weak negative correlation between DS and the current number of AEDs (SC, ρ = −0.228, $P = 3.83 \times 10^{-2}$; Table 1). Among Denver II domains, the strongest correlation with age at seizure onset was found between percentage of acquired gross motor skills (SC, ρ = 0.394, $P = 1.88 \times 10^{-4}$) and age at seizure onset, followed by fine motor skills (Spearman correlation, ρ = 0.338, $P = 1.54 \times 10^{-3}$) and language (SC, ρ = 0.253, $P = 2.08 \times 10^{-2}$; Table S5).

3.6 | Effect of a secondary variant

We explored the possibility that additional variants at other loci impacted correlations between age at seizure onset and DS. A total of 37 patients had at least one additional variant noted in their genetic report. These variants included those in other ion channels (eg, six individuals with a potassium channel variant and five individuals with an additional sodium channel variant), as well as in a number of other genes that have been implicated in epilepsy and other neurological disorders (Table S6). We repeated the correlation analyses dividing the patients into those with only a reported variant in *SCN8A* (8A; n = 49) and those with reported variants in *SCN8A* and one or more additional genes (8A+; n = 37). The correlation between age at seizure onset and DS increased for the 8A group (SC, ρ = *0*.452, $P = 1.11 \times 10^{-3}$), whereas no significant correlation was found for the 8A+ group (Table 1). Similarly, regarding the correlation with DS, only the 8A group maintained significant correlations with febrile seizures (positive), number of AEDs (negative), and seizure freedom (positive; Table 1). Among Denver II domains, significant positive correlations were maintained in the 8A group for all three subdomains mentioned above and also included a positive correlation with social skills. No significant correlations were found between percentage of acquired skills for the 8A+ group (Table S5).

3.7 | Effect of development delay before seizure onset

We divided the sample into those children who experienced delays prior to seizure onset and those who did not. We explored whether the above correlations persisted when we separately considered children who did—and did not—experience a delay prior to seizure onset. For the subset of the sample that did not experience a delay (n = 34), statistically significant correlations remained between age at seizure onset and DS (SC, ρ = 0.444, $P = 8.51 \times 10^{-3}$; Table 2). However, there were no statistically significant correlations between DS and seizure freedom, febrile seizures, or number of AEDs (Table 2). For the group that did experience delays prior to seizure onset (n = 27), the only statistically significant correlation was found between DS and seizure freedom (SC, ρ = 0.524, $P = 4.98 \times 10^{-3}$; Table 2).

As above, we subdivided these populations further by 8A or 8A+ status. For 8A patients who did not experience a delay prior to seizure onset (n = 17), the correlation was maintained between age at seizure onset and DS (SC, ρ = 0.703, $P = 1.65 \times 10^{-3}$; Table 2). On the other hand, 8A patients who did experience a delay prior to seizure onset (n = 18) exhibited no statistically significant correlations with age at seizure

TABLE 2 Correlations between seizure characteristics and development score for developmental patterns prior to seizure onset

	n	Seizure onset	Seizure freedom	Febrile seizures	AEDs, n
No delay prior to onset					
All patients	34	0.444*	0.050	0.311	−0.228
8A	17	0.703*	0.079	0.389	−0.301
8A+	17	0.070	0.080	na	−0.195
Delay prior to onset					
All patients	26	0.333	0.524*	0.061	−0.316
8A	18	0.365	0.458	na	−0.418
8A+	8	0.036	0.725**	0.285	0.404

Note: Correlations were analyzed with Spearman rank tests and are displayed above. Twenty-six patients were not included because parents were unsure whether there was a delay prior to onset. A value of "na" indicates that there was only one individual within the group with febrile seizures; thus, the correlation could not be computed.
Abbreviations: AED, antiepileptic drug; na, not applicable.
**P = <.01-.001, *P = .05-.01.

TABLE 3 Correlations between seizure characteristics and development score for developmental patterns at seizure onset

	n	Seizure onset	Seizure freedom	Febrile seizures	AEDs, n
No regression at onset					
All patients	46	0.502*	0.377**	0.246	−0.286
8A	28	0.646*	0.387***	0.383***	−0.373
8A+	18	−0.183	0.277	0.058	0.060
Regression at onset					
All patients	19	−0.039	0.032	0.430	0.470***
8A	11	0.072	−0.153	0.610***	0.602***
8A+	8	−0.334	0.0422	0.084	0.310
Regression + gained skills at onset					
All patients	21	0.527***	0.227	0.095	−0.717*
8A	10	0.554	0.424	na	−0.803**
8A+	11	0.545	0.060	0.103	−0.672***

Note: Correlations were analyzed with Spearman rank tests and are displayed above. A value of "na" indicates that there was only one individual within the group with febrile seizures; thus, the correlation value could not be computed.
Abbreviations: AED, antiepileptic drug; na, not applicable.
***P = <.001-0, **P = <.01-.001, *P = .05-.01.

onset or number of AEDs (Table 2). For 8A+ patients, there were no statistically significant correlations for those who did not (n = 9) experience a delay prior to seizure onset; however, there was a statistically significant correlation between seizure freedom and DS (SC, ρ = 0.725, $P = 2.71 \times 10^{-2}$).

3.8 | Effect of developmental regression at time of seizure onset

To test whether regression at the time of seizure onset affected neurodevelopmental outcome, we subdivided patients into groups that (1) did not regress, (2) regressed and regained skills, and (3) regressed and did not regain skills after seizure onset. Children who did not regress at seizure onset (n = 46) showed a positive correlation with onset age and DS (SC, ρ = 0.502, $P = 3.76 \times 10^{-4}$; Table 3). These cases also maintained a weak positive correlation between DS and seizure freedom (SC, ρ = 0.377, $P = 9.85 \times 10^{-3}$; Table 3). Similarly, patients who regressed and regained skills (n = 21) showed positive correlations for DS and seizure onset (SC, ρ = 0.527, $P = 1.41 \times 10^{-2}$). These cases lost the correlation between DS and seizure freedom (Table 3). However, this group yielded a stronger negative correlation between DS and number of currently administered AEDs (SC, ρ = −0.717, $P = 3.71 \times 10^{-4}$; Table 3). Patients who lost and did not regain skills (n = 19) showed statistically significant correlations only between number of currently administered AEDs and DS (SC, $\rho = 0.470$, $P = 4.23 \times 10^{-2}$; Table 3).

When we subdivided patients further by 8A or 8A+ status, the 8A group that did not regress at seizure onset (n = 28) maintained correlations between age at seizure onset and DS (Table 3). Whereas there was no correlation between DS and number of AEDs, there was a statistically significant correlation with seizure freedom (SC, $\rho = 0.387$, $P = 4.20 \times 10^{-2}$) and febrile seizures (SC, $\rho = 0.383$, $P = 4.42 \times 10^{-2}$). For the 8A+ group, there were no statistically significant correlations between age at seizure onset and DS or with any of the other tested categories (Table 3).

For the 8A population that regressed at seizure onset and did not regain skills (n = 11), there were statistically significant correlations between DS and number of AEDs and febrile seizures (Table 3). In the 8A+ population that regressed at seizure onset and did not regain skills (n = 8), there were no statistically significant correlations between DS and age at seizure onset or any of the other tested categories (Table 3). For the 8A and 8A+ populations that regressed and regained skills (n = 10 and 11, respectively), there were statistically significant negative correlations between number of AEDs and DS (Table 3). In some cases, correlations remained high, yet statistical significance was lost due to the small sample sizes.

4 | DISCUSSION

There is solid evidence that uncontrolled seizures in the developing brain have deleterious effects on cognition and behavior.[15] Although there are several previous studies examining the effect of such seizures in young patients with new onset epilepsy,[6,7,11,16] very few studies have been performed on patient cohorts with new onset epilepsy in the first year of life—when the brain is undergoing many critical periods of development.[10] The major aim of this study was to assess the strength of associations between seizure characteristics and the acquisition of neurodevelopmental skills in a cohort of children with SCN8A-related epilepsy, in which seizure onset occurs mainly within the first year of life. The current literature proposes that the underlying etiology of epilepsy plays an important, if not major, role in cognitive impairment.[15,17] By virtue of our cohort being limited to epilepsy patients with a variant deemed to be pathogenic in SCN8A, our study controls the contribution of variation in etiology. Notably, even within this cohort of patients with variants in a single gene, the cognitive/behavioral outcomes are quite heterogeneous.[3]

We assessed the acquisition of neurodevelopmental skills by using milestones listed in the Denver II test. Twenty of the 25 skills we examined are, on average, all acquired within the first 3 years of life, which encompass many critical periods of brain development. It is often difficult to distinguish the effects of seizures from underlying pathology, preexisting learning deficits, and effects of AEDs in retrospective studies.[11] We attempted to discover underlying causes of heterogeneity by subdividing the population, first by the number of variants in genetic testing reports, and subsequently by patterns of developmental regression before and at seizure onset.

Overall, the results showed that complex skills that are typically acquired later in development are the most delayed skills in children with SCN8A-related epilepsy (Figure 2A,B). Fine and gross motor skills that are learned in the first year of life were delayed by 4-8 months, whereas language (which is typically learned later) was delayed by 15.2 months (data not shown). We found that this increasing delay was associated with age at seizure onset. For example, ordinal logistic regression predicts that a 6-month delay in seizure onset would move a patient from the severe/moderate boundary to the moderate/mild boundary (Figure S1). Moreover, we obtained a statistically significant positive correlation between age at seizure onset and DS for the entire cohort (Table 1). This aligns with the current literature that supports the positive correlation between age at seizure onset and overall cognition and behavior.[6–11] However, although this correlation was maintained when we separately examined patients with a single reported *SCN8A* variant, it was lost in the group of patients who reported additional variants in genes other than *SCN8A*. This is despite most 8A patients being likely to have unknown/unreported variants at other genes. One possible explanation for this result is that variants in other genes may influence development in opposing manners (Figure 3A). For example, some variants may be beneficial modifiers and mitigate the deleterious effects of early onset of seizures, whereas other variants may augment the deleterious effects of SCN8A regardless of age at seizure onset. Many of the variants reported in the 8A+ group were found in other well-known ion channel genes (Table S6), and neuronal voltage-gated ion channels are known to be genetic modifiers of other forms of epilepsy.[18–20] This highlights the role other ion channels may play in modifying sodium channel effects, although further research is needed to fully understand whether specific ion channel variants might be beneficial or deleterious in cases of SCN8A-related epilepsy.

We found the occurrence and timing of initial developmental regression (ie, before or at seizure onset) altered correlations with DS. When we examined 8A children who had no delay prior to seizure onset, we found a positive correlation with age of seizure onset and DS (Table 2). Figure 3B illustrates this correlation under the assumption that 8A children attain developmental milestones relatively normally until seizures begin, and then onset seizures either cause or correspond to an initial brain insult that leads to delayed or reduced acquisition of developmental skills.

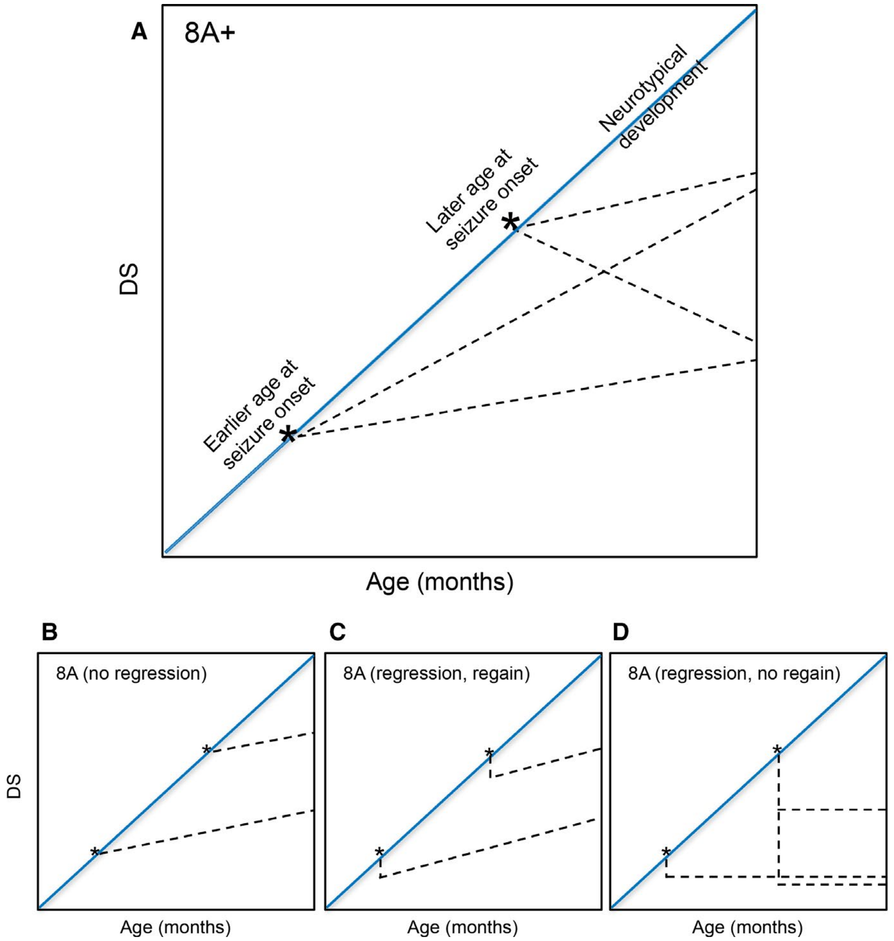

FIGURE 3 Schematic of model to explain correlations between age at seizure onset and development score (DS) under four scenarios. A, Lack of a correlation in the 8A+ group results when variants at other loci influence outcome in opposing directions. The diagonal blue line represents the trajectory of "neurotypical" development, and asterisks represent age at seizure onset. Dashed lines indicate a departure from neurotypical development. B, 8A cases with no regression or delay at time of seizure onset. Two dashed lines continue on an upward trajectory at a slower rate than for neurotypical development, with a lower DS resulting for an earlier age at onset. C, 8A cases with regression at seizure onset, followed by regaining of skills, are depicted with downward and upward sloping lines. This pattern results in a correlation between age at seizure onset and DS. D, 8A cases with regression at seizure onset without regaining skills. The dashed lines indicate a range of outcome that is independent of age at seizure onset

Interestingly, a positive correlation was maintained for children who regressed at seizure onset and regained these skills, yet was lost for those who regressed and did not regain skills (Figure 3C,D). One explanation for this pattern is that some children have an inherent resilience that permits them to regain and further acquire skills after initial loss due to seizure onset (Figure 3C), whereas others incur more severe damage at seizure onset that prevents further skill acquisition (Figure 3D).

It is important to note that 27 children in our cohort were reported to experience developmental delays prior to seizure onset. Therefore, seizures alone do not explain the onset of delays in all patients. Interestingly, the positive correlation between DS and current seizure freedom seen for the entire cohort was maintained in groups where seizures themselves were not found to be associated with delay (ie, delay before seizures and no regression at seizure onset). This suggests that whatever process causes nonseizure delays may be overcome in a subset of patients. Of note, the correlation with seizure freedom is not specific to having an *SCN8A* variant, but rather to having epilepsy. Under this model, seizure freedom (eg, as a result of pharmacological intervention) permits the child to regain skills and continue to make progress. Additional longitudinal studies are needed to measure the time course of this developmental progression and to better understand the possible mechanism(s) behind this finding.

Upon testing whether different initial seizure types were associated with better or worse developmental skill acquisition, we found a significant correlation only with febrile seizures. Febrile seizures are seizures that are associated with a fever and are relatively common (2%-5%) in young children.[21] Febrile seizures have been shown to have little cognitive effect on children, although recurrent febrile seizures have been suggested to interfere with normal language development.[22,23] We found a similar effect of febrile seizures in our 8A group, with those children having an average DS of 3.0, and their lowest acquired skillset was language, with 83% of language skills being acquired. The positive correlation between developmental skill acquisition and febrile seizures was seen in the 8A group that did and did not regress at seizure onset. Because febrile seizures themselves are a milder insult, the secondary outcome for these children is less severe than for those children experiencing a stronger or more impactful seizure type. This fits the model that seizures themselves are causing insults; however, the strength of these insults may play a role in overall developmental skill acquisition.

In epileptic patient populations, the administration of multiple AEDs can lead to a synergistic antiseizure effect; however, the combination of AEDs with different mechanisms of action may also increase risk of an adverse cognitive side effect.[24] Animal studies looking at the effect of AED on cognitive tasks after an induced seizure show mixed results, with some drugs having deleterious effects and others having beneficial effects.[16] Due to necessity of AED use for SCN8A children, we examined the impact of polytherapy (multiple AED use) in our cohort. A correlation was found in the 8A group that regressed at seizure onset and did and did not regain those skills. Interestingly, for those who regressed and did not regain skills, there was a positive correlation with the number of AEDs, whereas those who regressed and regained skills had a negative correlation. Therefore, children who regained skills are consistent with the hypothesis that AEDs have a negative effect on development; although these children regained lost skills, they were not able to gain new skills to further their developmental progress. Those who did not gain skills do not fit into this hypothesis, but it is possible that the onset of seizures was more severe, thus requiring more AEDs for seizure control to allow for some developmental progress to occur.

5 | LIMITATIONS AND CONCLUSIONS

We have shown statistically significant pairwise correlations for neurocognitive development in a cohort of SCN8A patients using an online registry database. Despite these promising results, there are several limitations. First, because our questionnaire was completed by parents or caregivers, there is a potential for respondent recall error.[25] However, to assess consistency of the questionnaire, we compared results from a similar survey taken by 51 of the same participants 1 year prior to the current questionnaire and found the data to be highly concordant between the 2 years (Table S7). Of note, we indirectly acquired information for the Denver II from parents/caregivers who were asked whether their child had acquired a set of skills (yes/no). These skills were chosen from the Denver II test utilizing the timescale provided by the test to determine the 90th percentile cutoffs. Additionally, the variables analyzed in this study were chosen to minimize bias that could produce false positives. For example, the answers to questions were either easily obtained from genetic and clinician reports or based on questions typically asked by a clinician at the first visit. Analyses of these data are less likely to inflate positive correlations, and as such our positive correlation results are likely to be conservative.

We acknowledge that additional unreported variants are likely present within our 8A cohort. To the extent this is true, our correlation results are likely to be conservative. Future studies would benefit from exome sequence data as an inclusion criterion to more comprehensively categorize patients. It is also likely that individual *SCN8A* variants have varying levels of pathogenicity. Our sample size is too small to have any statistically significant tests that would result from further stratifying our cohort based on mutational type or subphenotypes. However, it is important to note this research presents the largest cohort of children with *SCN8A* variants[5,26] and is the first paper to conduct correlative analyses on the SCN8A population.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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